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Circadian Variation in Metabolism and Inflammation: Role in Obesity-Induced Heart Failure with Preserved Ejection Fraction

**Fadhel A. Alomar¹, Jaipaul Singh²,
Ram B. Singh^{3,*}, and Keshore R. Bidasee^{4,5}**

¹Department of Pharmacology and Toxicology,
College of Clinical Pharmacy, Imam Abdulrahman Bin
Faisal University, Dammam, Saudi Arabia

²School of Natural Sciences, University of Central
Lancashire, Preston, UK

³Medical Hospital and Research Centre, Centre
of Nutrition & Heart Research, Moradabad, India

⁴Department of Pharmacology and Experimental
Neuroscience; Department of Environment
and Occupational Health, University of Nebraska
Medical Center, Omaha, NE, Lincoln NE, USA

⁵Nebraska Redox Biology Center, Lincoln NE, USA

Introduction and Aim

Obesity has become a public global health problem. More than 13% of the world's 7.8 billion people (11% of men and 15% of women) are obese, defined as having a body mass index above 30 kg/m². In North America and several Middle Eastern Countries, more than 30% of adults are obese. The alarming problem is that children as young as twelve years of age are now becoming obese. Obesity with high-fat and high-sugar diets is a risk factor for type 2 diabetes mellitus (T2DM), hypertension and early-onset heart failure (HF) with preserved ejection fraction (HFpEF) that leads to frequent hospitalizations. It is possible that diet, inactivity and other modern lifestyle factors may have an important role in the development of heart failure, either with or without decrease in ejection fraction [1]. This mini review discusses whether circadian oscillations in metabolism and inflammation could be responsible for the time-of-day-dependence of adverse cardiovascular events in patients with HFpEF by increasing production of cytotoxic α -dicarbonyl species methylglyoxal (MG) and by decreasing expression of the primary MG-degrading enzyme glyoxalase-1 (Glo1), respectively.

Review and Conclusion

There is much evidence in the literature that periconceptional, perinatal nutritional factors as well dietary fatty acids in later life after birth are important in the pathogenesis of cardiovascular diseases (CVDs) [2-5]. Increased consumption of saturated, monounsaturated or n-6 polyunsaturated fatty acids

* Correspondence: Dr. Jaipaul Singh.
Email: jSingh3@uclan.ac.uk

has also shown beneficial effects in rodent studies [2]. This effect is associated with decline in inflammation and improved resistance to mitochondrial permeability transition. The underlying mechanisms are complex and may be due to cardiac adaptation, in particular when diets rich in saturated fat are administered. A more thorough knowledge is necessary to comprehend the effects of various fatty acids on cardiac phospholipids, lipid metabolites and metabolic flux in the normal and failing heart. Increased intake of high-sugar and high-fat diet may cause obesity-induced expression of Glo1 under inflammatory conditions, which may blunt accumulation of MG with circadian clock dysfunction of the cardiomyocyte and fibroblast.

It is proposed that the presence of other nutrients such as flavonoids, coenzyme Q10 and ω -3 fatty acids decrease the lipotoxic effects of saturated fat and slow the progression of hypertrophy, resulting in HFpEF,

rather than HFrEF. It is clear that alterations in dietary fat intake may have promise in the management of HF. The effects of diet on cardiac cells may depend on various biomarkers that are known to damage cardiomyocytes. Increase in ceramides due to high glucose or fast food diets, high levels of trimethylamine N-oxide (TAMO) due to increased intake of red meat and eggs (choline and lecithin) as well as increase in advanced glycation products due to high-fat diets are new biomarkers of cardiac hypertrophy. These markers should be prevented by new therapies, which can avoid the development of cardiac hypertrophy as well as HFpEF. Cohort studies and animal experiments are needed to determine the role of healthy diet in terms of saturated, monounsaturated and n-6 polyunsaturated fatty acids intake for this group of vulnerable population (see Figure 1).

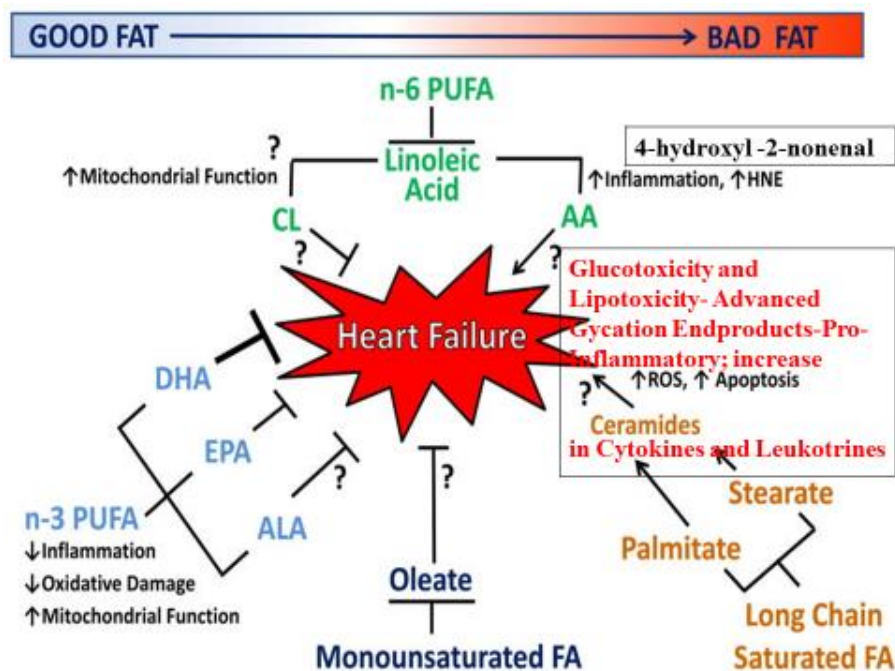


Figure 1. Modified flow diagram depicting the potential underlying mechanisms of how high-fat and high-glucose diets predispose to the development and progression of heart failure.

Specific pharmacologic agents to treat HFpEF are non-existent, in part because it is a diagnosis of exclusion, if speckle tracking echocardiography is not available. Recent advances in imaging have demonstrated that early cardiac dysfunction may be identified in a stage of pre-heart failure, which may be

indicative of HFpEF. Clinical studies targeting the renin-angiotensin-aldosterone system (RAAS) to attenuate key co-morbidities associated with HFpEF, including endothelial cell dysfunction, vascular stiffening, impaired myocardial relaxation, fibrosis and improved vascular perfusion, have shown only

modest decreases in hospitalization rates and adverse clinical outcomes, suggesting that activation of RAAS may not be a primary cause. The severity of adverse cardiovascular events in patients with HFpEF exhibits a time-of-day-dependence. It is possible that circadian oscillations in metabolism and inflammation could be responsible for the time-of-day-dependence of adverse cardiovascular events in patients with HFpEF by increased circadian production of cytotoxic α -dicarbonyl species methylglyoxal (MG) and by decreasing expression of the primary MG-degrading enzyme glyoxalase-1 (Glo1), respectively. It is clear that any antioxidant agent such as higher intake of omega-3 and monounsaturated fatty acids and flavonoids administered as chronotherapy may enhance Glo1 release, leading to decline in MG and improvement in cardiac function.

In brief, it is possible that an increase in the expression of Glo1 under inflammatory conditions may blunt accumulation of MG and reset the circadian clock function of the cardiomyocyte and fibroblast, which could serve as a novel therapeutic strategy to attenuate the development of HFpEF [6].

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